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# Isochromosome Xq in Klinefelter Syndrome: Report of 7 New Cases

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**In this collaborative study we report on 2 prenatally and 5 postnatally diagnosed cases with a 47,X,i(Xq),Y chromosomal constitution. Excepting tall stature, the 5 adult patients showed all typical manifestations of Klinefelter syndrome. Taken together with previously reported cases, these data suggest that Klinefelter syndrome with isochromosome Xq has a favorable prognosis with normal mental development, and with normal-to-short stature. The prevalence of this Klinefelter variant is calculated to be between 0.3–0.9% in males with X chromosome polysomies.** 

**KEY WORDS: Klinefelter syndrome, isochromosome Xq, short stature**

## INTRODUCTION

Numerical variants of the 47,XXY chromosomal constitution in patients with Klinefelter syndrome (KS) have been described in 20% of all cases [De Grouchy and Turleau, 1982], including various mosaic forms with variable clinical manifestations. On the other hand, only a few patients show structural rearrangements of an X chromosome [Chandra et al., 1971; Nielsen et al., 1976; Patil et al., 1981; Fryns, 1982; Zelante et al., 1991]. Recently we detected two fetuses with a karyotype of 47,X,i(Xq),Y in prenatal diagnosis. Reports on KS with an isochromosome Xq have been mentioned only briefly in the literature and, therefore, genetic counseling is difficult in such cases. Although most of these patients show the main manifestations of KS, there is a suggestion of some clinical differences between these men and 47,XXY KS patients, most noticeably in lack of height increase [Richer et al., 1989]. Due to the small number of reported patients with a 47,X,i(Xq),Y karyotype, it is probable that the clinical spectrum has not been fully elucidated.

Only through evaluation of a larger group of such patients may genetic counseling be provided from a more secure basis than at present after prenatal diagnosis. In this collaborative presentation we report on 2 fetuses with 47,X,i(Xq),Y, and summarize the data on 5 adult patients with KS and an isochromosome Xq.

## PRENATAL CASES

### Case A

A 33-year-old gravida I woman was referred for prenatal diagnosis. Her husband was 36 years old at the time of investigation. Amniocentesis was carried out at 13 weeks of gestation. The alpha-fetoprotein level was normal. The cytogenetic analysis showed a 47,X,i(Xq),Y karyotype in 16 metaphases by GTG-banding studies. The supernumerary isochromosome X was apparently monocentric, as indicated by CBG-banding. After genetic counseling, the pregnancy was terminated upon the parents' request at 16 weeks of gestation. A subsequent cytogenetic analysis was performed on fetal tissue and confirmed the cytogenetic findings. There was no indication of mosaicism.

### Case B

A 35-year-old gravida I woman was referred for amniocentesis because of advanced maternal age. She had had one previous spontaneous abortion. The husband was 36 years old. Amniocentesis was performed at 17 weeks of gestation. The alpha-fetoprotein level was normal. The chromosomal analysis of 18 metaphases from amniotic fluid cell cultures demonstrated a 47,X,i(Xq),Y karyotype. After genetic counseling the parents decided to continue the pregnancy. At term, an apparently normal male infant was delivered (birth weight 4,000 g, birth length 54 cm). Further examination showed unilateral symbrachydactyly and absence of the ipsilateral pectoralis major muscle, which was diagnosed as Poland syndrome. The patient's psychomotor development and external genitalia are normal.

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## POSTNATAL CASES

These 5 patients were referred for cytogenetic evaluation between 1980–1994. In all cases the indication for diagnosis was infertility suggesting Klinefelter syndrome. At the time of referral, age of patients ranged from 21–41 years.

Chromosome studies on cultured lymphocytes showed a karyotype of 47,X,i(Xq),Y in all cases. A mean of 28 metaphases was scored for each individual, and there was no indication of mosaicism. All isochromosomes were apparently monocentric, and studies of DNA replication patterns in 2 cases have shown the i(Xq) to be invariably late-replicating. Material for further molecular studies was not available. All patients showed small testes, azoospermia, and elevated plasma follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Androgen levels were low in 3 cases, and within normal range in 2 cases. One patient presented with gynecomastia. Height ranged from 170.5–181 cm (Table I, cases 12–16). All patients appeared to have normal intelligence and intellectual capacities.

## DISCUSSION

Isochromosome Xq is the most common structural aberration in patients with Ullrich-Turner syndrome [Schmid et al., 1974], but is apparently rare in males. Up to now, 11 patients with i(Xq) have been reported, including one mosaic with a 47,XXY/48,XX,i(Xq),Y complement (Table I). Apart from these cases, it was noted that all patients show the main clinical manifestations of KS, including infertility, decreased virilization, gynecomastia, and elevated plasma FSH and LH levels. This was also observed in the 5 patients presented here, and demonstrates that these characteristics of KS result from additional Xq material only, without additional Xp material. It has been shown by observations on other structural anomalies of X chromosomes that the presence of additional material of Xq11→q22 causes azoospermia and hormonal imbalance in males [Nielsen et al., 1976; Patil et al., 1981; Fryns, 1982].

The only clinical difference between the 47,XXY and 47,X,i(Xq),Y KS patients which has been reported is normal-to-short stature in the latter [Donlan et al., 1987; Richer et al., 1989]. It is well-documented that 47,XXY males show a mean increase in height of about 6.5 cm in comparison with their male relatives [Varrela, 1984]. The difference between 47,XXY males and the subsample of 47,X,i(Xq),Y is difficult to validate, since only few data from male relatives are documented in the latter group (Table I). However, normal-to-short stature seems to be substantiated if the mean height of 4 patients from the present sample (cases 12–15) is compared with age-matched normal controls from the same ethnic population (mean 174.4 cm vs. 176.0 cm) [Grabski et al., 1979].

This implies that increase in height, as seen in 47,XXY males, is associated with additional Xp material. Tall stature has also been noted in a patient with KS and an isodicentric Xq, who carried three copies of Xp [Zelante et al., 1991]. Recent association studies between short stature and terminal deletions of both Xp and Yp have pointed to putative growth gene(s) located

TABLE I. Clinical Features in 16 Patients With Klinefelter Syndrome With Isochromosome Xq*

| Case no. | Reference | Age (years) | Height (cm) | Weight (kg) | Gynecomastia | Intelligence | LH level | FSH level | Testosterone level | Karyotype |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Zang et al., 1969 | 44 | 176 | 84 | Slight | Normal | nr | nr | nr | 47,X,i(Xq),Y |
| 2 | Gardiner et al., 1978 | 36 | 164.5 | nr | None | Normal | Elevated | Elevated | Low | 47,X,i(Xq),Y |
| 3 | McDermott, 1978 | 29 | 163 | 53 | nr | nr | nr | nr | nr | 47,X,i(Xq),Y |
| 4 | Kalousek et al., 1978 | 24 | 166.4 | 78 | None | Normal | Elevated | Elevated | Low | 47,X,i(Xq),Y |
| 5 | Trunca et al., 1979 | 32 | nr | nr | Slight | nr | Elevated | Elevated | Low | 47,X,i(Xq),Y |
| 6 | Ponzio et al., 1980 | 33 | 168 | 63 | Slight | Normal | Elevated | Elevated | Low | 47,X,i(Xq),Y |
| 7 | Geneix et al., 1981 | 31 | 166 | 57 | None | Normal | nr | Elevated | nr | 47,X,i(Xq),Y |
| 8 | Donlan et al., 1987 | 17 | 160[a] | 60 | Yes | Normal | Elevated | Elevated | Low | 47,X,i(Xq),Y |
| 9 | Kleczkowska et al., 1988 | 28 | 198 | 89 | nr | nr | Elevated | Elevated | Low | 47,X,i(Xq),Y |
| 10 | Kleczkowska et al., 1988 | 18 | 164.5 | 57 | nr | nr | nr | Elevated | nr | 47,XXY/48,XX,i(Xq),Y |
| 11 | Richer et al., 1989 | 30 | 165[b] | 59 | None | nr | Elevated | Elevated | Normal | 47,X,i(Xq),Y |
| 12 | Present case 1 | 28 | 175 | 75 | Yes | Normal | Elevated | Elevated | Low | 47,X,i(Xq),Y |
| 13 | Present case 2 | 21 | 171 | 66 | None | Normal | Elevated | Elevated | Normal | 47,X,i(Xq),Y |
| 14 | Present case 3 | 41 | 170.5 | 77 | None | Normal | Elevated | Elevated | Low | 47,X,i(Xq),Y |
| 15 | Present case 4 | 37 | 181[c] | 64 | None | Normal | Elevated | Elevated | Low | 47,X,i(Xq),Y |
| 16 | Present case 5 | 40 | 168 | nr | None | Normal | Elevated | Elevated | Normal | 47,X,i(Xq),Y |

*nr, not reported.
[a]Mother, 160 cm; father, 188 cm.
[b]Mother, 148 cm; father, 170 cm; brothers, 180 cm, 183 cm.
[c]Mother, 165 cm; father, 181 cm; brother, 181 cm.

in the pseudoautosomal Xp/Yp region near the telomere [Ogata et al., 1992]. Comparisons of mean adult height in patients with sex chromosome aberrations indicate that the growth disadvantage caused by quantitative alteration of euchromatic or noninactivated regions may be relevant to statural development [Ogata and Matsuo, 1993]. These findings suggest that differences in adult height in both 47,XXY and 47,X,i(Xq),Y males, as well as in other sex chromosome aberrations, might be explained by loss of growth gene(s) and varying degrees of chromosomal imbalance.

The most probable origin of Xq isochromosomes is misdivision of the centromere or sister-chromatid exchange of one X chromosome. The isochromosomes in all 7 cases described here were apparently monocentric. Molecular studies of Xq isochromosomes in Ullrich-Turner syndrome demonstrated either heterozygosity at some loci on Xq in maternally derived chromosomes, or the presence of Xp material in some other cases [Lorda-Sanchez et al., 1991]. This demonstrates the origin of Xq isochromosomes by interchanges between homologous X chromosomes, or the formation of isodicentric X chromosomes by X;X translocations, neither of which can be distinguished by conventional cytogenetic methods. However, the pseudoautosomal regions in Xp are lacking in such isodicentrics. The finding of a 47,X,i(Xq),Y chromosome complement seems to be rare in prenatal diagnosis. So far, only one case of a 46,XY/47,X,i(Xq),Y mosaic has been reported [Alliet et al., 1989]. Due to the limited number of cases, the prevalence of this Klinefelter variant is still unclear. The observation of an isochromosome Xq in 2 patients in a total of 569 males with KS suggests that i(Xq) chromosome formation may be detected in approximately 1 of 250 males with X chromosome polysomy and KS [Fryns et al., 1990]. The 5 adult men described here were diagnosed in the present collaborative effort among 574 males with KS between 1980–1994. The prevalence is more than twice as high (0.87%) in our series than that reported by Fryns et al. [1990] (0.35%). This observation emphasizes that the frequency of isochromosome Xq in patients with KS may be higher than hitherto considered.

The delineation of the phenotype of subjects with isochromosome Xq KS is essential to provide meaningful genetic counseling after prenatal diagnosis. As shown above, 47,X,i(Xq),Y patients show most of the main clinical manifestations expected in males with classical KS. Most probably, the occurrence of Poland anomaly in one newborn (case B) is not related to the abnormal karyotype, since no similar abnormality has been observed in any of the adult cases. Moreover, all 47,X,i(Xq),Y patients are reported to have normal intelligence, although it must be taken into account that these patients were not diagnosed on the indication of behavior problems but because of infertility or hypogonadism.

In conclusion, observations on 16 adult patients support the view that the presence of an isochromosome Xq in KS has a favorable prognosis in terms of normal mental development and normal stature.

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